REMARKS

Claims 30-34, 37-39, 41-48, 50-56, and 63-74 were examined and finally rejected by the Examiner under 35 U.S.C. § 103(a) as obvious over the combination of Mollison (US 6,015,815) in view of Kulkarni (US 5,387,589) and Hu (US 5,800,807) in the Final Office Action mailed August 4, 2010. The Examiner has not addressed the traversal of the withdrawal from consideration of Claims 75, 122-125, 127-130, 132, and 134 for allegedly being directed to non-elected subject matter. Applicants again request that Claim 75 be restored to non-withdrawn status and Claims 122-125, 127-130, 132, and 134 be examined for the reasons stated in the Amendment of May 17, 2010 at page 9.

Applicants request pre-appeal brief review of the rejections of the pending claims because there are clear errors in the Examiner's rejections. The clear errors include:

1. The combination of cited references fails to provide a reasonable expectation of success that rapamycin can be used to treat age-related macular degeneration or inhibit the transition from the dry form of age-related macular degeneration to the wet form.

2. The combination of cited references fails to teach or suggest a composition containing polyethylene glycol suitable for injection in the eye.

3. The combination of cited references fails to provide a reasonable expectation of success in using a polyethylene glycol composition for injection into the eye

To support a *prima facie* case of obviousness the Examiner must articulate the prior art source and a reason for combining the art to teach or suggest all of the limitations of a claim. *See* M.P.E.P. § 2143. Furthermore, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02.* Applicants respectfully submit that the claims are not obvious for at least reasons that the cited references do not teach each and every limitation of the claims and fail to provide a reasonable expectation of success for arriving at the claimed invention.

A. The combination of cited references fails to provide a reasonable expectation of success that rapamycin can be used to treat age-related macular degeneration or inhibit the transition from the dry form of age-related macular degeneration to the wet form

The Examiner has not addressed Applicants' arguments regarding independent method Claims 51 and 63, which are respectively drawn to treating the wet form of age-related macular

degeneration by administering rapamycin into the eye, and inhibiting the transition of the dry form of age-related macular degeneration to the wet form by administering rapamycin into the eye. Mollison teaches to use tetrazole-containing compounds that are chemically distinct from rapamycin. Mollison teaches that these compounds can be used to treat not less than about 175 distinct diseases or conditions, including diseases as diverse as gastric ulcers and gingivitis. *See* column 8, line 51 to column 10, line 64. No one of skill in the art would actually believe that the tetrazole-containing compounds of Mollison could be used to treat all of these diseases or conditions. Nonetheless, even taking this disclosure at face value, it does not teach that rapamycin would be useful for all these indications. When rapamycin is discussed in the background section of Mollison, the only diseases it is associated with are fungal infections, tumors, multiple sclerosis, rheumatoid arthritis, and organ graft rejection.

Importantly, several of the significant side effects caused by rapamycin (*e.g.*, acne and thrombocytopenia) are conditions that Mollison teaches are treated by the tetrazole-containing compounds. *See Amendment of May 17, 2010*, page 10, and Exhibit A submitted therewith. Thus, one of skill in the art would know that rapamycin ***cannot*** be used to treat all of the indications listed in Mollison. As such, the skilled artisan would have no reasonable expectation of success in using rapamycin to treat the wet form of age-related macular degeneration or inhibit the transition of the dry form of age-related macular degeneration to the wet form based on the teachings of Mollison. Based on known side effects of rapamycin being included in the disease list of Mollison, the art actually collectively teaches away from using rapamycin for all of the diseases in Mollison. Moreover, none of the cited art teaches inhibiting the transition of the dry form of age-related macular degeneration to the wet form as recited in Claims 63-67 with any compound, let alone rapamycin. The Examiner has not responded to the merits of these arguments.

B. The combination of cited references fails to teach or suggest a composition containing polyethylene glycol suitable for injection in the eye

Independent Claims 30 and 38 recite a composition comprising rapamycin and polyethylene glycol suitable for ophthalmic administration by injection. Independent Claim 39 recites a composition comprising an active agent such as rapamycin in combination with

polyethylene glycol suitable for ophthalmic administration by injection. Independent Claims 51 and 63 recite methods of treatment comprising administering a composition comprising rapamycin and polyethylene glycol into the vitreous or between the conjunctiva and the sclera of an eye. None of the cited art, alone or in combination, teach or suggest all of these recited features.

The Examiner takes the position that Mollison teaches the addition of polyethylene glycol to rapamycin. *Office Action of August 4, 2010*, page 2. The Examiner specifically refers to column 12. However, column 12 relates to compositions that contain the tetrazole-containing compounds of Mollison and not rapamycin. *See* Mollison, column 11, lines 49-50 ("The pharmaceutical compositions of the present invention comprise a compound of the invention ...") and Applicants arguments in the *Amendment of October 2, 2008*, pages 9-11. Furthermore, Mollison only teaches to use polyethylene glycol in compositions "for parenteral injection," in "[s]olid dosage forms for oral administration," in "[l]iquid dosage forms for oral administration," and in "[c]ompositions for rectal or vaginal administration." Mollison, column 11, lines 64-65; column 12, line 52; column 13, line 24; and column 14, line 18. In contrast, for "[t]opical administration ... to the ... surfaces of the ... eye," Mollison teaches to use "ophthalmic vehicles" including "an ointment, vegetable oil or an encapsulating material." Mollison, column 13, line 46-47 and column 14, lines 15-17. In summary, Mollison teaches to use polyethylene glycol for many compositions including those for parenteral, oral, rectal, and vaginal administration but conspicuously ***omits polyethylene glycol for ophthalmic compositions***. Accordingly, Mollison fails to teach a composition including polyethylene glycol suitable for opthalmic administration by injection and does not teach injection of such a composition into the vitreous or between the conjunctiva and the sclera of an eye. The Examiner merely assumes that compositions in Mollison that include polyethylene glycol are suitable for opthalmic injection despite citing no reference that provides such a teaching or suggestion.

Although the Examiner appears to no longer rely on Hu and instead argues again that Mollison teaches polyethylene glycol as a carrier for rapamycin, Applicants also submit that Hu fails to teach the limitations missing from Mollison. Hu is directed to the use of demulcents (i.e., an agent that forms a film over the outer membrane of the eye). Thus, Hu only teaches topical

administration to the eye, not a composition that is suitable for administration by injection as featured in the claims.

Accordingly, Applicants respectfully submit that the cited art fails to teach or suggest all limitations of the claims.

C. The combination of cited references fails to provide a reasonable expectation of success in using a polyethylene glycol composition for injection into the eye

In addition to the fact that the combination of Mollison, Kulkarni, and Hu does not teach or suggest all of the features of the claims, the cited references also fail to provide a reasonable expectation of success for arriving at the claimed compositions and methods. Polyethylene glycol was known to be an eye irritant at the time of the invention, as indicated by the polyethylene glycol Material Safety Data Sheet (MSDS) submitted as Exhibit A in the Amendment of July 10, 2009. The Examiner has not refuted that a person of ordinary skill in the art at the time of the invention would be manifestly discouraged from making and using a composition including polyethylene glycol for injection in the eye.

Moreover, Applicants filed a Declaration of Dr. David Weber pursuant to 37 C.F.R. § 1.132 with the Amendment of May 17, 2010. Based on Dr. Weber's declaration, one of ordinary skill in the art would have considered a polyethylene glycol composition ***unsuitable*** for administration into the eye. Dr. Weber states that those of skill in the ophthalmic arts would not have used a hygroscopic agent such as polyethylene glycol for administration into an eye. Specifically, if such a composition was administered into the vitreous, it would have been expected to pull water into the eye ball leading to a deleterious increase in intraocular pressure and desiccation of retinal tissues. If the composition was administered by subconjunctival injection, it would have been expected to pull water out of the eye ball, leading to a deleterious decrease in intraocular pressure and swelling. Thus, as Dr. Weber states, one of skill in the art would not have used polyethylene glycol for administration into the eye over concerns of disruption of vision or damage to the eye. Furthermore, Dr. Weber points out that all compositions that are currently administered into the eye are aqueous based. Finally, Dr. Weber notes that one of skill in the art would have been disinclined to use polyethylene glycol for

ophthalmic injection because it would have been expected to require a large gauge needle creating a hole into the eye.

Despite the foregoing statements from Dr. Weber which show the cited references and knowledge in the field at the time of the invention provide no reasonable expectation of success, the Examiner has not substantively rebutted Dr. Weber's points, but instead improperly shifted the burden on Applicants to provide evidence of the advantages of using polyethylene glycol. *Final Office Action of August 4, 2010* at page 2. However, it is well settled that the Examiner "bears the initial burden of presenting a *prima facie* case of unpatentability..." *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). Until the Examiner has established a *prima facie* case of obviousness, the Applicants need not present arguments or evidence of non-obviousness.

CONCLUSION

Based on the foregoing, Applicants request withdrawal of the rejection of Claims 30-34, 37-39, 41-48, 50-56, and 63-74 under 35 U.S.C § 103(a) because the cited art fails to establish a *prima facie* case of obviousness. The cited references do not teach each of the claimed features and also provides no reasonable expectation of success. Applicants also request that Claim 75 be restored to non-withdrawn status and Claims 122-125, 127-130, 132, and 134 be examined.

Applicants have requested review of the pending rejections. If after review, the panel should find any remaining impediment to allowing one or more of the claims, Applicants respectfully request the panel decision specifically address any such remaining rejection(s) to permit Applicants to determine any necessary follow up actions. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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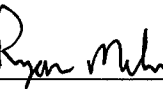
By: 

Ryan E. Melnick
Registration No. 58,621
Attorney of Record
Customer No. 20995
(858) 836-9000